

### AMENDMENTS TO THE CLAIMS

Please amend claims 1-3, 5, 7, 9-11, 13-16, 19, 20, 22-24, 26, 27, 29, and 31-33, and cancel claims 17 and 18, as set forth below.

The current listing of claims replaces all prior listings.

1. (Currently Amended) A method to detect binding of a first specific binding pair member to a second specific binding pair member, comprising:

a) associating a first unlabeled specific binding pair member with a surface-enhanced Raman scattering-active particle or substrate;

b) contacting the first unlabeled specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate with a second unlabeled specific binding pair member; and

c) detecting binding of the second unlabeled specific binding pair member to the first unlabeled specific binding pair member by detecting a difference in a surface-enhanced Raman scattering signal of the first unlabeled specific binding pair member before contacting the first unlabeled specific binding pair member with the second unlabeled specific binding pair member and after contacting the first unlabeled specific binding pair member with the second unlabeled specific binding pair member, wherein the surface-enhanced Raman scattering signal is generated by excitation of the first unlabeled specific binding pair member associated with the surface-enhanced Raman scattering-active particle or substrate, thereby detecting binding of the first specific binding pair member to the second specific binding pair member.

2. (Currently Amended) The method of claim 1, wherein the surface-enhanced Raman scattering-active particle or substrate associated with the first unlabeled specific binding pair member is a metal particle.

3. (Currently Amended) The method of claim 2, wherein the first unlabeled specific binding pair member is associated with the metal particle by adsorbing the first unlabeled specific binding pair member to the surface-enhanced Raman scattering surface.

4. (Original) The method of claim 3, wherein the metal particle comprises colloidal silver or gold.
5. (Currently Amended) The method of claim 3, wherein the first unlabeled specific binding pair member is immobilized on an immobilization substrate prior to associating with the surface-enhanced Raman scattering-active surface.
6. (Original) The method of claim 1, wherein the difference in the surface-enhanced Raman scattering signal is a decrease in the signal.
7. (Currently Amended) The method of claim 6, wherein binding of the second unlabeled specific binding pair member to the first unlabeled specific binding pair member dissociates the first unlabeled specific binding pair member from the metal particle.
8. (Original) The method of claim 1, wherein the difference in the surface-enhanced Raman scattering signal is an increase in the signal.
9. (Currently Amended) The method of claim 3, wherein adsorption is detected before the second unlabeled specific binding pair member is contacted with the first unlabeled specific binding pair member.
10. (Currently Amended) The method of claim 9, wherein adsorption is detected by detecting an increase in a surface-enhanced Raman scattering signal generated by the first unlabeled specific binding pair member after contacting the first unlabeled specific binding pair member with the metal particle.
11. (Currently Amended) The method of claim 3, wherein the first unlabeled specific binding pair member is associated with the metal particle in the presence of a chemical salt.
12. (Original) The method of claim 11, wherein the chemical salt is lithium chloride.
13. (Currently Amended) The method of claim 1, wherein the first unlabeled specific binding member is a protein and the second unlabeled specific binding pair member is a protein.

14. (Currently Amended) The method of claim 13, wherein the first or second unlabeled specific binding pair member is an antibody molecule, or fragment thereof.

15. (Currently Amended) The method of claim 1, wherein the first unlabeled specific binding pair member is a receptor and the second unlabeled specific binding pair member is a ligand.

16. (Currently Amended) The method of claim 1, wherein the first or second unlabeled specific binding pair member is a nucleic acid molecule and the other of the first or second unlabeled specific binding pair member is a protein.

17. (Canceled)

18. (Canceled)

19. (Currently Amended) The method of claim 16[[8]], wherein surface enhanced coherent anti-Stokes Raman spectroscopy is used to detect the first unlabeled specific binding pair member.

20. (Currently Amended) The method of claim 1, wherein the first unlabeled specific binding pair member is associated with the surface-enhanced Raman scattering-active particle or substrate by immobilizing the first specific binding pair member on a surface-enhanced Raman scattering-active substrate.

21. (Original) The method of claim 20, wherein the surface-enhanced Raman scattering-active substrate comprises a porous silicon substrate comprising impregnated metals.

22. (Currently Amended) A method to detect binding of an antibody, or fragment thereof, to an antigen, comprising:

- a) immobilizing an unlabeled antibody on an immobilization substrate;

b) contacting the immobilized unlabeled antibody with a metal particle to adsorb the immobilized unlabeled antibody on the metal particle;

c) contacting the immobilized unlabeled antibody with an unlabeled antigen; and

d) detecting binding of the unlabeled antigen to the unlabeled antibody, or fragment thereof, by detecting a difference in a surface-enhanced Raman scattering signal generated by the unlabeled antibody before contacting the unlabeled antibody with the unlabeled antigen and after contacting the unlabeled antibody with the unlabeled antigen, wherein the surface-enhanced Raman scattering signal is generated by excitation of the surface-enhanced Raman scattering-active particle or substrate, thereby detecting binding of the unlabeled antibody to the unlabeled antigen.

23. (Currently Amended) The method of claim 22, wherein the unlabeled antibody, ~~or fragment thereof~~, is a whole unlabeled antibody molecule.

24. (Currently Amended) The method of claim 22, wherein the unlabeled antibody, or fragment thereof, is an unlabeled Fab fragment.

25. (Original) The method of claim 22, wherein the metal particle comprises colloidal gold or silver.

26. (Currently Amended) A method to detect an analyte in a biological sample, comprising:

a) immobilizing a first specific unlabeled binding pair member on a surface, wherein the first unlabeled specific binding pair member binds ~~[[the]]~~ an unlabeled analyte;

b) contacting the immobilized first unlabeled specific binding pair member with a metal particle to adsorb the immobilized first unlabeled specific binding pair member on the metal particle;

c) contacting the immobilized first unlabeled specific binding pair member adsorbed on the metal particle with the biological sample; and

d) detecting a surface-enhanced Raman scattering signal generated by excitation of the metal particle adsorbed by the immobilized first unlabeled specific binding pair member before contacting the immobilized first unlabeled specific binding pair member with the ~~second~~

unlabeled analyte ~~specific binding pair member~~ and after contacting the first unlabeled specific binding pair member with the unlabeled analyte ~~second specific binding pair member~~, wherein a difference in the detected surface-enhanced Raman scattering signals is indicative of the presence of the analyte in the biological sample.

27. (Currently Amended) The method of claim 26, wherein the first unlabeled specific binding pair member is an unlabeled antibody, or fragment thereof.
28. (Original) The method of claim 26, wherein the metal particle comprises colloidal gold or silver.
29. (Currently Amended) The method of claim 26, wherein the first unlabeled specific binding pair member is adsorbed on the metal particle in the presence of lithium chloride.
30. (Original) The method of claim 26, wherein the biologic sample comprises serum.
31. (Currently Amended) A method to detect an antibody or a fragment thereof, comprising:
  - a) immobilizing ~~[[the]]~~ an unlabeled antibody, or fragment thereof, on a surface;
  - b) contacting the unlabeled antibody, or fragment thereof, with a metal particle to adsorb the immobilized unlabeled antibody on the metal particle; and
  - c) detecting a surface-enhanced Raman scattering signal generated by excitation of the metal particle adsorbed by ~~of~~ the immobilized unlabeled antibody, or fragment thereof, thereby detecting the unlabeled antibody, or fragment thereof.
32. (Currently Amended) The method of claim 30, wherein the unlabeled antibody, ~~or fragment thereof~~, is a whole antibody molecule.
33. (Currently Amended) The method of claim 30, wherein the unlabeled antibody, or fragment thereof, is an unlabeled Fab fragment.
34. (Original) The method of claim 30, wherein the metal particle comprises colloidal gold or silver.